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A Phase Ib Dose-Escalation Study of the Oral Pan-PI3K Inhibitor Buparlisib (BKM120) in Combination with the Oral MEK1/2 Inhibitor Trametinib (GSK1120212) in Patients with Selected Advanced Solid Tumors

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Abstract

Purpose: MAPK and PI3K/AKT/mTOR pathways play important roles in many tumors. In this study, safety, antitumor activity, and pharmacokinetics of buparlisib (pan class PI3K inhibitor) and trametinib (MEK inhibitor) were evaluated.

Experimental Design: This open-label, dose-finding, phase Ib study comprised dose escalation, followed by expansion part in patients with *RAS*- or *BRAF*-mutant non–small cell lung, ovarian, or pancreatic cancer.

Results: Of note, 113 patients were enrolled, 66 and 47 in dose-escalation and -expansion parts, respectively. MTD was established as buparlisib 70 mg + trametinib 1.5 mg daily [5/15, 33% patients with dose-limiting toxicities (DLT)] and recommended phase II dose (RP2D) buparlisib 60 mg + trametinib 1.5 mg daily (1/10, 10% patients with DLTs). DLTs included stomatitis (8/103, 8%), diarrhea, dysphagia, and creatine kinase (CK) increase (2/103, 2% each). Treatment-related grade 3/4 adverse events (AEs) occurred in 73 patients (65%); mainly CK increase, stomatitis, AST/ALT (aspartate aminotransferase/alanine aminotransferase) increase, and rash. For all (21) patients with ovarian cancer, overall response rate was 29% [1 complete response, 5 partial responses (PR)], disease control rate 76%, and median progression-free survival was 7 months. Minimal activity was observed in patients with non–small cell lung cancer (1/17 PR) and pancreatic cancer (best overall response was SD). Relative to historical data, buparlisib exposure increased and trametinib exposure slightly increased with the combination.

Conclusions: At RP2D, buparlisib 60 mg + trametinib 1.5 mg daily shows promising antitumor activity for patients with *KRAS*-mutant ovarian cancer. Long-term tolerability of the combination at RP2D is challenging, due to frequent dose interruptions and reductions for toxicity. *Clin Cancer Res; 21(4); 730–8. ©2014 AACR.*

Introduction

The MAPK and the PI3K/AKT/mTOR (PI3K) pathways are frequently dysregulated in cancer. Molecular alterations in these pathways are implicated in tumorigenesis and resistance to anticancer therapies (1). *KRAS* mutations are found most frequently in pancreatic cancer (70%–90%; ref. 2), non–small cell lung cancer (NSCLC; 20%–30%; ref. 3), and colorectal cancer (30%–40%; ref. 4), whereas *BRAF* mutations occur in approximately 8% of human tumors, most frequently in melanoma (40%–60%; ref. 5), thyroid (39%), colorectal cancer (12%), and ovarian cancers (12%; ref. 6).

MAPK and PI3K pathways converge at multiple points, and preclinical data suggest that dual blockade may be synergistic (1, 7, 8), thus providing a rationale for evaluating safety, tolerability, and efficacy of PI3K and MEK inhibitor combinations in patients with tumors bearing genetic aberrations of these pathways.

Buparlisib (BKM120) is a potent and highly specific oral pan-class I PI3K inhibitor that does not inhibit mTOR and Vps34 kinases (9). MTD and recommended phase II dose (RP2D) of single-agent oral buparlisib are 100 mg/d (10). Key toxicities include hyperglycemia, neuropsychiatric disorders, liver toxicity, skin rash and hypersensitivity, and gastrointestinal toxicity. Trametinib (GSK1120212; Mekinist) is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity (11, 12). MTD and RP2D of trametinib are 3 and 2 mg/d,

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

The MAPK and PI3K/AKT/mTOR (PI3K) pathways are frequently dysregulated in many cancers. Molecular alterations in these pathways, including *KRAS* mutations, are implicated in tumorigenesis and resistance to anticancer therapies. These pathways converge at multiple points, and preclinical data suggest that dual blockade may be advantageous, providing a rationale for evaluating safety, tolerability, and efficacy of PI3K and MEK inhibitor combinations in patients with tumors bearing genetic aberrations of these pathways. This article demonstrates clinical activity in patients with ovarian cancer who are treated with a combination of buparlisib (PI3K inhibitor) and trametinib (MEK inhibitor). Furthermore, it appears that subtypes of ovarian cancer may be disposed to react differently, with *KRAS* G12V-mutated versions seeming to benefit more from combination treatment. As ovarian cancer is still a disease for which there is large unmet medical need, further studies to investigate these findings are recommended, including extensive biomarker analysis.

respectively (13, 14). Key toxicities include rash, gastrointestinal effects, cardiac and vascular disorders, ocular toxicities, and interstitial lung disease. Trametinib has been approved as monotherapy for unresectable or metastatic *BRAF* V600E/K mutation-positive melanoma in the United States and Canada.

The aim of this phase Ib study was to determine MTD and/or RP2D for buparlisib combined with trametinib when administered orally to adult patients with selected advanced solid tumors, and then to evaluate safety and preliminary antitumor activity of MTD and/or RP2D in patients with advanced NSCLC, ovarian cancer, or pancreatic cancer with *RAS* or *BRAF* mutations in the expansion part of the study (clinicaltrials.gov registry identifier NCT01155453).

Materials and Methods

Study design and patient population

This phase Ib study was conducted at 7 hospitals across 5 countries in the United States, Canada, and Europe. Accrual period was May 2010 to January 2013. Dose-escalation part enrolled adult patients with advanced solid tumors harboring *RAS* or *BRAF* mutations such as colorectal cancer, melanoma, NSCLC, triple-negative breast cancer (TNBC), or pancreatic cancer. When MTD was defined, dose-expansion part was conducted in adult patients with measurable and evaluable (by RECIST version 1.0) advanced NSCLC, ovarian, or pancreatic cancer with *RAS* or *BRAF* mutations. Patients had baseline World Health Organization (WHO) performance status (PS) 0 to 2, and adequate organ function. Patients with anxiety assessed as grade $\geq$3 [National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4] or ocular/retinal comorbidities associated with increased risk of central serous retinopathy or retinal vein occlusion were excluded. Prior treatment, including PI3K or MEK inhibitor therapy, was permitted if it had ended at least 4 weeks (or >1 cycle) before initiating study medication. Treatment was discontinued in cases of unacceptable toxicity, disease progression, at discretion of the investigator or by patient withdrawal.

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol was approved by an Institutional Review Board at each hospital, and all patients provided written informed consent before any study procedures.

Procedures

Buparlisib capsules and trametinib tablets were coadministered orally once daily in a 28-day cycle. First cohort received 30 mg/d of buparlisib + 0.5 mg/d trametinib. Doses were escalated according to an adaptive Bayesian logistic regression model (BLRM) with overdose control principle until MTD and/or RP2D was reached (Fig. 1A and B; refs. 15, 16). Dose escalation could not exceed MTD of either agent as monotherapy, and only one drug was escalated at a time. Cohorts of 3 to 6 evaluable patients were enrolled per dose combination. Multiple dose combinations could be studied simultaneously. Primary endpoint was incidence rate of dose-limiting toxicities (DLT) in cycle 1. DLT was defined as an adverse event (AE) or abnormal laboratory value assessed as at least possibly related to study medication, which also met the prespecified DLT criteria. AEs were classified according to NCI CTCAE version 4. Dose modifications were permitted for treatment-related toxicity. All patients underwent ophthalmologic examinations at baseline, each cycle completion, end of study, and as clinically warranted. Secondary objectives were safety, pharmacokinetics (PK), efficacy, and predictive/pharmacodynamic (PD) biomarkers. Tumor response was classified according to RECIST version 1.0.

Blood samples for serial PK evaluation for both buparlisib and trametinib were collected on days 1, 15, and 28 of cycle 1 in dose-escalation part; and on day 28 of cycle 1 in expansion part.

Archival and fresh tumor tissue samples, whenever feasible, were collected at baseline and at cycle 1 day 28 (dose-escalation part) or at baseline and day 15 (dose-expansion part) to investigate PD effects on molecular signaling, a secondary objective, and to evaluate potential biomarkers predictive of efficacy, an exploratory objective. Assessments included biomarker status/levels pre- versus posttreatment for PD and antitumor effect, S6 (p-S6) and ERK (p-ERK) phosphorylation, measured by immunohistochemistry (IHC). In addition, exploratory molecular alteration analysis on markers relevant to PI3K and MAPK pathways, such as PTEN protein expression and *PIK3CA* alteration, was completed on tumor tissue via IHC and next-generation sequencing, respectively.

Statistical analysis

The BLRM was fitted on the cycle 1 DLT data accumulated throughout the dose escalation to model the dose-toxicity relationship of buparlisib and trametinib when given in combination. At each decision time point, the adaptive BLRM identified combinations that meet the Escalation with Overdose Control criteria so that only combinations associated with a risk of excessive toxicity less than 25% could be considered for the next dose cohort. Dose recommendations were based on posterior summaries for each dose combination, including the mean, median, SD, 95% credibility interval, and the interval probabilities for under dosing (DLT rate >0.16), targeted (DLT rate between 0.16 and 0.35), and excessive toxicity (DLT rate > 0.33). A clinical synthesis of available toxicity information (including AEs that were not DLTs and laboratory tests), PK, PD, and efficacy information, as well as recommendations from the

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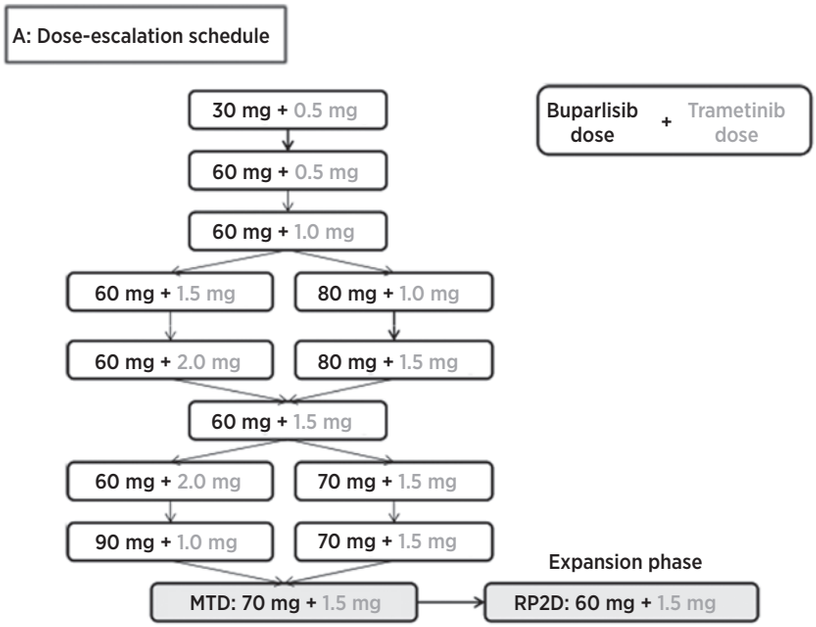

Figure 1.
Dose-escalation schedule and DLTs during dose-escalation part.

Cohort #	Buparlisib	Trametinib	N[1]	N[2]	DLT	Nature of DLT[3]
1	30 mg	0.5 mg	4	4	0	—
2	60 mg	0.5 mg	5	5	0	—
3	60 mg	1.0 mg	6	6	1	G3 stomatitis
4.1	60 mg	1.5 mg	5	5	1	G3 type II diabetes, G3 hyperlipasemia
4.2	80 mg	1.0 mg	4	4	0	—
5.1	60 mg	2.0 mg	4	4	1	G3 stomatitis
5.2	80 mg	1.5 mg	6	5	3	G3 CK elevation, 20% LVEF decrease, G3 nausea, G3 decreased appetite, G3 decreased oral intake
6	60 mg	1.5 mg	6	5	0	—
7.1	60 mg	2.0 mg	5	4	0	—
7.2	60 mg	1.5 mg	4	4	1	G3 stomatitis, G3 dysphagia
8.1	70 mg	1.5 mg	6	6	4	G3 CK elevation, skipped/delayed dose (G2 dysphagia, G2 diarrhea)
8.2	90 mg	1.0 mg	5	5	1	Skipped/delayed dose (G2 stomatitis)
9	70 mg	1.5 mg	6	5	0	—
All			66	62	12	

As of July 18, 2013.
1 - Number of patients treated:
2 - Number of evaluable patents.
3 - Patients may have more than one DLT.
G - grade; CK - creatine kinase; LVEF - left ventricular ejection fraction.

BLRM, were used to determine dose combination for the next cohort. Investigators, Novartis and GSK trial personnel participated in decision making. Selected doses could not violate overdose criteria. AEs, overall response rates (ORR), disease control rate (DCR), progression-free survival (PFS), duration of stable disease (SD), and overall survival (OS) were summarized.

Results

As of July 18, 2013, 113 patients were enrolled and treated with buparlisib and trametinib; all included in safety and efficacy analyses. Baseline characteristics are summarized in Table 1. Nine combination dose levels were explored during dose escalation, varying from 30 to 90 mg for buparlisib and 0.5 to 2.0 mg for trametinib in a total of 66 patients (Fig. 1A and B). MTD was defined as 70 mg buparlisib and 1.5 mg trametinib. The BLRM indicated that estimated DLT rate at MTD and RP2D were 23% and 18%, respectively, and the posterior risk of DLT rate being in the excessive toxicity category was less than 0.1% for both MTD and RP2D, and thus met the EWOC criteria. Twelve (19%) of 62 evaluable patients during dose escalation experienced DLTs, all of which were reversible (Fig. 1B).

There were 5 of 15 (33%) evaluable patients with DLTs in the MTD cohort and 1 of 10 (10%) in the RP2D cohort. Most frequent DLTs among all evaluable patients were stomatitis (8/103, 8%), diarrhea, dysphagia, and creatine kinase (CK) increase (2/103, 2% each).

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Table 1. Baseline characteristics of patients enrolled

Demographics	Dose escalation *N* = 66	Dose expansion *N* = 47	All patients *N* = 113
A. All patients			
Age at baseline, y, Median (range)	57.0 (29.0–84.0)	56.0 (25.0–72.0)	56.0 (25.0–84.0)
Sex, *n* (%)			
Male	30 (45.5)	19 (40.4)	49 (43.4)
Female	36 (54.5)	28 (59.6)	64 (56.6)
WHO performance status, *n* (%)			
0	29 (43.9)	16 (34.0)	45 (39.8)
1	37 (56.1)	30 (63.8)	67 (59.3)
2	0	1 (2.1)	1 (0.9)
Primary tumor type, *n* (%)			
CRC	33 (50.0)	0	33 (29.2)
Pancreatic	9 (13.6)	15 (31.9)	24 (21.2)
Cutaneous melanoma	9 (13.6)	0	9 (8.0)
Ovarian	4 (6.1)	17 (36.2)	21 (18.6)
TNBC	4 (6.1)	0	4 (3.5)
NSCLC	2 (3.0)	15 (31.9)	17 (15.0)
Other[a]	4 (6.1)	0	4 (3.5)
Missing	1 (1.5)	0	1 (0.9)
Local molecular status[b]			
KRAS mutation	41 (62.1)	43 (91.5)	84 (74.3)
NRAS mutation	6 (9.1)	0	6 (5.3)
BRAF mutation	9 (13.6)	3 (6.4)	12 (10.6)
Number of prior antineoplastic regimens, *n* (%), Median (range)	3 (1–8)	3 (1–14)	3 (1–14)

Demographics	Ovarian cancer patients (*N* = 21)
B. Ovarian cancer patients	
Age at baseline, y, median (range)	49.0 (25.0–68.0)
WHO performance status, *n* (%)	
0	11 (52.4)
1	10 (47.6)
2	0
Histologic grade, *n* (%)	
Well differentiated	15 (71.4)
Moderately differentiated	3 (14.3)
Poorly differentiated	2 (9.5)
Undifferentiated	—
Unknown	1 (4.8)
Details of tumor histology/cytology, *n* (%)	
Adenocarcinoma	3 (14.3)
Papillary serous/serous adenocarcinoma	13 (61.9)
Mucinous adenocarcinoma	1 (4.8)
Clear cell adenocarcinoma	1 (4.8)
Other	3 (14.3)
Stage at initial diagnosis, *n* (%)	
Stage I (a–c)	6 (28.6)
Stage II (a–c)	3 (14.3)
Stage III	5 (23.8)
Stage III (a–c)	7 (33.3)
Stage IV	—
Local molecular status[b]	
KRAS mutation	19 (90.5)
BRAF mutation	1 (4.8)
Number of prior antineoplastic regimens, *n* (%), median (range)	3 (1–14)

Abbreviation: CRC, colorectal cancer.

[a]Includes 1 patient with thyroid cancer, 1 patient with ampullary cancer, 1 patient with choroid melanoma of the eye, and 1 patient with endocervical cancer.

[b]During dose-escalation part, patients with pancreatic cancer or TNBC irrespective of mutation status were enrolled. One patient with granulosa cell tumor of the ovary with a RASA1 mutation was enrolled during the dose-expansion phase.

MTD was initially used during expansion part; however, after review of tolerability of first 10 patients enrolled, this dose was revised because of high incidence of AEs (mainly stomatitis and rash). On the basis of the Bayesian inference of the dose–DLT relationship using DLT information from patients enrolled in the dose-escalation part, as well as patients enrolled at the MTD level in dose-expansion part, the BLRM estimated that combination dose of 60 mg buparlisib with 1.5 mg trametinib satisfies the EWOC criteria, and this dose was established following review of available data as RP2D. All new patients were subsequently enrolled to the starting dose of RP2D of 60 mg buparlisib and 1.5 mg trametinib. In total, 47 patients were treated during dose expansion.

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A total of 110 (97%) patients experienced AEs considered by investigators to be treatment related. Overall, 73 (65%) of 113 patients experienced treatment-related grade 3/4 AEs; most frequent (>5%) were CK increase (16/113, 14%), ALT (alanine aminotransferase) increase, and stomatitis (10/113, 9% each), maculo-papular rash and macular rash (9/113, 8% each), AST (aspartate aminotransferase) increase (7/113, 6%), thrombocytopenia, and dermatitis acneiform (6/113, 5% each; Table 2). Incidence of treatment-related grade 3/4 AEs at MTD and RP2D were 82% (28 AEs) and 58% (23 AEs), respectively.

Serious AEs (SAE) related to treatment were experienced by 21 of 113 (19%) patients; most frequent were stomatitis (5/113, 4%) and diarrhea (4/113, 4%). At MTD and RP2D, 9 (27%) and 5 (13%) of 40 patients, respectively, experienced treatment-related SAEs. No treatment-related deaths were observed.

Thirty-five (31%) of 113 patients permanently discontinued study drugs due to AEs, most common of which were ALT increase and rash macular (4/113, 4% each). At MTD and RP2D, 15 (44%) and 8 (20%) patients, respectively, discontinued study treatment due to AEs. AEs requiring dose interruption and/or dose reductions were experienced by 79 patients (70%) overall, of which most frequently reported (≥10%) were stomatitis (18/113, 16%), CK increase (15/113, 13%), and ALT increase (14/113, 12%). At MTD and RP2D, 29 (85% and 73%, respectively) patients, reported AEs requiring dose interruption and/or dose reductions.

At the MTD, 20 patients (58.8%) treated with buparlisib and 22 patients (64.7%) treated with trametinib had a relative dose intensity ≥75%. At the RP2D, 39 patients (97.5%) treated with buparlisib and 26 patients (65%) treated with trametinib had a relative dose intensity ≥75%.

Pharmacokinetics

Buparlisib was absorbed rapidly following oral administration (median T_{max} was 2.17 (1.0–12.3) hours at RP2D on cycle 1 day 15. After reaching peak plasma drug concentration (C_{max}), buparlisib concentrations decreased in a biexponential manner. At RP2D, geometric mean values of C_{max} and AUC0-24 on cycle 1 day 1 and cycle 1 day 15 were 340.87 ng/mL [coefficient of variation (CV)% 50.80] and 3,106.81 ng·h/mL (CV% 32.29) and 522 ng/mL (CV% 50.1), and 6,607 ng·h/mL (CV% 32.3), respectively. Geometric mean values of the accumulation ratio on cycle 1 day 15 and day 28 at RP2D dose level were found to be 2.12 (CV% 47.04) and 2.05 (CV% 48.88), respectively (Fig. 2).

The plasma concentration–time profile of trametinib also showed rapid absorption with a median T_{max} of 2.95 (1.5–12.3) hours at RP2D on cycle 1 day 15 (Fig. 2). Geometric means of C_{max} and AUC0-24 after a single dose at RP2D were 3.36 ng/mL (CV% 69.10) and 29.60 ng·h/mL (CV% 33.56). Geometric mean values of C_{max} and AUC0-24 on cycle 1 day 15 at RP2D and at MTD for C_{max} were 19 ng/mL (CV% 33.3), and 16 ng/mL (CV% 159.5), and for AUC0-24 were 325 ng·h/mL (CV% 32.2), and 391 ng·h/mL (CV% 50.1), respectively. Geometric mean values of the accumulation ratio on cycle 1 day 15 and day 28 at RP2D dose level were found to be 9.95 (CV% 28.55) and 10.37 (CV% 23.99), respectively. Steady state was achieved within 15 days for both drugs.

Table 2. Treatment-related AEs occurring in ≥5% of patients overall (all grades and grades 3–4; at RP2D, MTD, and overall)

	Buparlisib 60 mg + trametinib 1.5 mg (*N* = 40) *n* (%) Grades		Buparlisib 70 mg + trametinib 1.5 mg (*N* = 34) *n* (%) Grades		All patients (*N* = 113) *n* (%) Grades	
Preferred term	**All**	**3–4**	**All**	**3–4**	**All**	**3–4**
Total	39 (97.5)	23 (57.5)	33 (97.1)	28 (82.4)	110 (97.3)	73 (64.6)
Dermatitis acneiform	16 (40.0)	1 (2.5)	22 (64.7)	4 (11.8)	58 (51.3)	6 (5.3)
Diarrhea	18 (45.0)	0	23 (67.6)	4 (11.8)	55 (48.7)	5 (4.4)
Blood CK increased	20 (50.0)	6 (15.0)	17 (50.0)	6 (17.6)	51 (45.1)	16 (14.2)
Stomatitis	17 (42.5)	2 (5.0)	17 (50.0)	5 (14.7)	46 (40.7)	10 (8.8)
Nausea	13 (32.5)	0	9 (26.5)	0	35 (31.0)	2 (1.8)
Rash macular	9 (22.5)	1 (2.5)	11 (32.4)	7 (20.6)	29 (25.7)	9 (8.0)
Rash maculo-papular	11 (27.5)	2 (5.0)	10 (29.4)	2 (5.9)	29 (25.7)	9 (8.0)
Vomiting	11 (27.5)	0	9 (26.5)	0	28 (24.8)	0
AST increased	8 (20.0)	3 (7.5)	6 (17.6)	1 (2.9)	22 (19.5)	7 (6.2)
Fatigue	11 (27.5)	2 (5.0)	5 (14.7)	0	22 (19.5)	2 (1.8)
ALT increased	6 (15.0)	2 (5.0)	7 (20.6)	3 (8.8)	20 (17.7)	10 (8.8)
Dry skin	7 (17.5)	0	10 (29.4)	0	20 (17.7)	0
Hyperglycemia	4 (10.0)	2 (5.0)	3 (8.8)	0	19 (16.8)	3 (2.7)
Decreased appetite	8 (20.0)	0	5 (14.7)	0	18 (15.9)	2 (1.8)
Asthenia	4 (10.0)	1 (2.5)	6 (17.6)	1 (2.9)	17 (15.0)	3 (2.7)
Hypertension	4 (10.0)	1 (2.5)	6 (17.6)	1 (2.9)	12 (10.6)	2 (1.8)
Pruritus	0	0	9 (26.5)	2 (5.9)	11 (9.7)	3 (2.7)
Thrombocytopenia	3 (7.5)	1 (2.5)	6 (17.6)	4 (11.8)	11 (9.7)	6 (5.3)
Skin fissures	6 (15.0)	0	4 (11.8)	0	10 (8.8)	0
Dysphagia	2 (5.0)	0	5 (14.7)	1 (2.9)	8 (7.1)	1 (0.9)
Face edema	3 (7.5)	0	4 (11.8)	0	8 (7.1)	0
Edema peripheral	4 (10.0)	0	2 (5.9)	0	8 (7.1)	0
Dysgeusia	3 (7.5)	0	3 (8.8)	0	7 (6.2)	0
Lipase increased	5 (12.5)	3 (7.5)	1 (2.9)	1 (2.9)	7 (6.2)	4 (3.5)
Abdominal pain	2 (5.0)	0	1 (2.9)	0	6 (5.3)	0
Rash	1 (2.5)	0	1 (2.9)	0	6 (5.3)	0
Xerosis	1 (2.5)	0	1 (2.9)	1 (2.9)	6 (5.3)	2 (1.8)

Abbreviation: CK, creatine phosphokinase.

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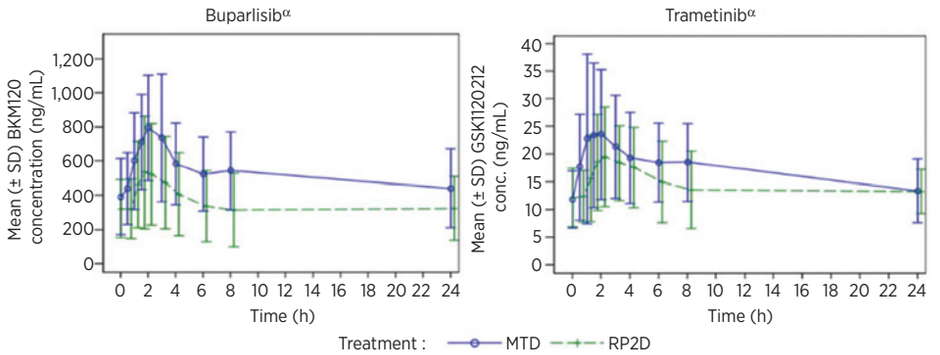

Figure 2.
PK: plasma concentration–time profiles of buparlisib and trametinib after repetitive oral combination dosing of buparlisib and trametinib—cycle 1 day 15.

Antitumor activity and pharmacodynamics

Of 113 evaluable patients in the study, 7 [6.2%; 90% confidence interval (CI), 2.9–11.3; 6 ovarian and 1 NSCLC patients harboring *KRAS* mutations] had a best response of partial or complete responses (PR or CR).

Of the 21 patients with ovarian cancer, 4 were enrolled in the dose-escalation phase and 17 in the dose-expansion phase (Table 1A). The majority were well-differentiated serous cancer (15 patients, 71%) and were *KRAS* mutated (19 patients, 91%); Table 1B summarizes additional characteristics. These patients were heavily pretreated with median of three prior lines of therapy (range, 1–14). ORR was 29% (1 confirmed CR, 5 confirmed PR) and 50% at RP2D (1 confirmed CR and 3 confirmed PR; Table 3). An additional 2 (10%) of 21 patients experienced a best target lesion reduction of at least 30% without subsequent confirmation of response (one progressed, and the second underwent resection of nontarget lesion; Fig. 3A). DCR was 76% and median duration of SD was 11 months. Median PFS in all patients with ovarian cancer was 7 months (95% CI, 4.2–12.9). At time of analysis data cutoff date, median OS was not reached as a majority (18 patients, 86%) of patients with ovarian were alive. Three patients were continuing on study treatment as of July 18, 2013; one patient with ovarian cancer and CR subsequently progressed in December 2013 at cycle 15, 1 patient with NSCLC with SD progressed in August 2013 after 8 cycles and the third patient with ovarian cancer and SD was still ongoing on cycle 19 as of June 2014.

Of the 17 patients with NSCLC, 9 (53%) achieved a best overall response (BOR) of SD and 1 (6%) patient with *KRAS* mutation attained confirmed PR (Fig. 3A). One additional patient with NSCLC (6%) experienced a best percentage reduction of 54% in sum of longest diameters (SLD) without subsequent confirmation of the response criterion (Fig. 3A). Median PFS was 4 months (95% CI, 1.8–5.3) and median OS was 5 months (95% CI, 3.9–NA). For the patients with pancreatic cancer, 12 (50%) achieved a BOR of SD. Median PFS was 2 months (95% CI, 1.8–3.4) and median OS was almost 5 months (95% CI, 3.8–5.8).

Multiple linear regression models were performed to estimate the association with the best percentage change in SLD. There was no statistically significant exposure–response relationship, potentially due to the limited number of patients treated. Treatment duration exposure data of patients who started at MTD or RP2D dose illustrated that most responders had a durable response despite reductions from the starting dose (Supplementary Figs. S2 and S3).

For the PD assessment, a reduction in expression of p-S6 and p-ERK was observed relative to baseline. Overall, mean percentage change in the cytoplasmic levels of p-S6-240, p-S6-235, and p-ERK from baseline at cycle 1 day 28 was −25% ($n = 8$), −14% ($n = 8$), and −34% ($n = 4$), respectively. Highest inhibition of pS6-235 was observed in 2 patients with ovarian cancer (56.2% and 48.1% decrease from baseline, respectively), both were partial responders. There was no evidence of strong corresponding p-S6-240 or p-ERK inhibition and one of these 2 partial responders showed even increase of p-ERK levels when on study treatment. Overall, it was not possible to determine any association between efficacy and PD markers, possibly due to limited available data (Supplementary Fig. S1A–S1C).

Exploratory analyses examined any relationship between molecular status at baseline and efficacy (Fig. 3A and B). Although not statistically significant, patients with ovarian cancer with a *KRAS* G12V alteration appeared to be more responsive to study treatment compared with patients with other alterations (Fig. 3B). These analyses were hypothesis generating, and outcome should be interpreted cautiously because of small sample size with further study needed to confirm. No clear associations between

Table 3. Patients ovarian cancer: BOR

BOR	Buparlisib 60 mg + trametinib 1 mg (*N* = 1) *n* (%)	Buparlisib 60 mg + trametinib 1.5 mg (*N* = 8) *n* (%)	Buparlisib 70 mg + trametinib 1.5 mg (*N* = 12) *n* (%)	All patients (*N* = 21) *n* (%)
CR	0	1 (12.5)	0	1 (4.8)
PR	0	3 (37.5)	2 (16.7)	5 (23.8)
SD	0	2 (25.0)	8 (66.7)	10 (47.6)
Progressive disease	0	1 (12.5)	1 (8.3)	2 (9.5)
Unknown	1 (100.0)	1 (12.5)	1 (8.3)	3 (14.3)
ORR (CR or PR)	0	4 (50.0)	2 (16.7)	6 (28.6)
DCR (CR or PR or SD)	0	6 (75.0)	10 (83.3)	16 (76.2)

Abbreviation: SD, stable disease, defined as at least one SD assessment (or better) >6 weeks after start of treatment (and not qualifying for CR or PR).

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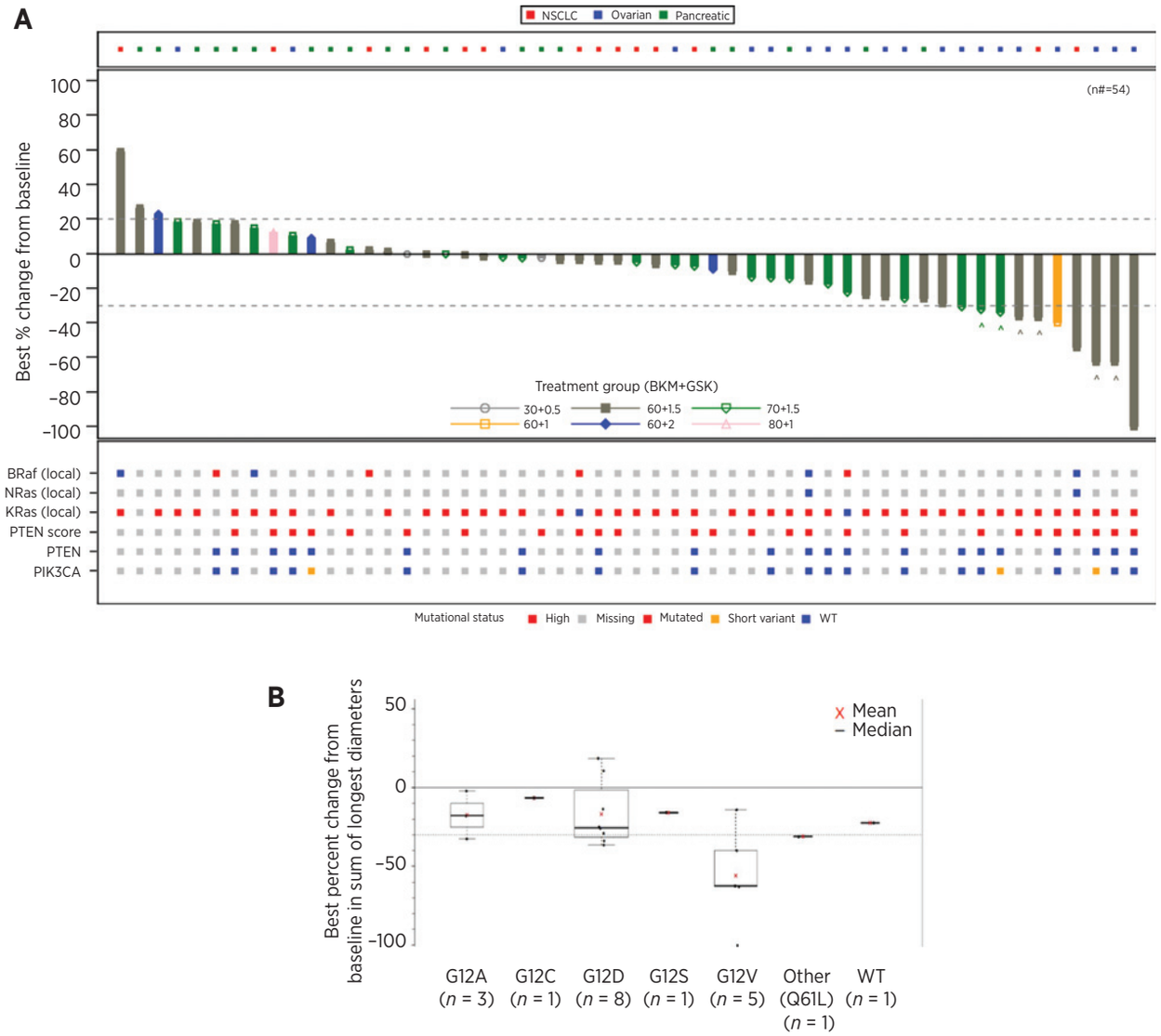

Figure 3.
Efficacy results. A, best percentage change from baseline in sum of longest diameters as per investigator assessment by local and central mutational status for patients with NSCLC, ovarian, or pancreatic cancer as primary tumor type. #Patients with missing best percentage change from baseline are not included. Short variant: sequence insertion, sequence deletion, or point mutation. Mutated: local molecular alteration. *, complete response, ^, partial response. B, boxplot of best percentage change from baseline in sum of longest diameters as per investigator assessment for patients with ovarian cancer by local *KRAS* mutation status and location.

markers relevant to PI3K and MAPK pathways and clinical activity were found (Fig. 3A).

Discussion

This phase 1b study demonstrated that oral pan-PI3K inhibitor buparlisib and oral MEK1/2 inhibitor trametinib can be safely combined with an RP2D of buparlisib 60 mg and trametinib 1.5 mg daily in patients with *BRAF*/*RAS*-mutant solid tumors. The relative dose intensity reflected better tolerability with RP2D compared with MTD of the combination. However, long-term treatment was very challenging for both dose combinations. Other PI3K and MEK inhibitor combination studies have shown similar toxicity profiles to this study, with fatigue, gastrointestinal, and cutaneous toxicity being most predominant (17–22), limiting ability to administer both agents at the single-agent MTDs in combination.

Exposure and maximum concentration of buparlisib appeared to be lower than in the first-in-man (FIM) study (CBKM120X2101; ref. 10) both after a single dose and at steady state, although the accumulation ratios of AUC0-24 on days 15 and 28 were similar to what was observed in monotherapy, suggesting that this decrease might be due to a change in bioavailability. Similar phenomenon was observed in other combination trials; however, the underlying mechanism is unknown.

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Exposure of trametinib appeared to be increased in the combination compared with the 2 mg dose in the FIM study (13), whereas no major change in its maximum concentration was observed. Accumulation of trametinib is highly variable making it difficult to establish if this increased exposure is due to a potential interaction with buparlisib. When comparing known PK characteristics of the two drugs, no clear mechanism could be identified for a potential interaction.

Preliminary results in other PI3K and MEK inhibitor combination studies have shown early signs of antitumor activity in colorectal cancer, renal cell carcinoma, ovarian cancer, NSCLC, endometrial cancer, melanoma, and prostate cancer (17, 19–21). In a recent phase I trial testing SAR245409 (PI3K/mTOR inhibitor) combined with pimasertib in 46 patients, there were two PRs with the combination (*KRAS*-mutated colorectal cancer with neuroendocrine features and *KRAS*/*PIK3CA*–mutated low-grade ovarian cancer; ref. 19).

In our study, promising antitumor activity [ORR 29% (at RP2D ORR was 50%), DCR 76%, and median PFS 7 months] was observed in *RAS*/*BRAF*–mutant ovarian cancer. In a phase II study of single-agent MEK inhibitor selumetinib in 52 patients with low-grade serous ovarian carcinoma, CR or PR was observed in 8 patients (15%), SD was observed in 34 patients (65%), and median PFS was 11.0 months (23). There were 14 of 34 (41%) patients with *KRAS* mutations, of which 2 (14%) showed a tumor response; this was not significantly different from the 25% response rate in *KRAS* wild-type tumors (5/20 patients; $P = 0.672$); however, median PFS in patients with ovarian cancer with *KRAS* mutations was not reported (23). Two ongoing trials are investigating MEK inhibitors in low-grade serous ovarian cancer: A phase III study with single-agent MEK inhibitor binimetinib (MEK162, MILO study) and a phase II/III study with trametinib.

Alternative dosing schedules of this combination might improve long-term tolerability. Currently, a phase 1b, open-label study (CMEK162X2109) is evaluating an alternative schedule of the PI3Kα inhibitor BYL719 combined with MEK inhibitor binimetinib MEK162 (MEK162 given 14 days on, followed by 7 days off and continuous dosing of BYL719) in patients with *RAS*- or *BRAF*-mutant advanced solid malignancies, such as ovarian cancer.

It has been shown that targeting the PI3K/AKT/mTOR pathway seldom works when a single agent is used (24). The current generation of PI3K inhibitors is designed to produce more specific inhibition and potentially improve toxicity profiles, although none are currently approved for treatment of ovarian cancer. Activation of these pathways and role played in promoting ovarian cancers are not completely understood (25). Results of our study indicate that buparlisib and trametinib combination treatment can inhibit PI3K and MAPK pathway signaling, although it is unclear if the degree of suppression achieved with plasma concentrations delivered is sufficient for sustained pathway blockade.

Our findings demonstrate clinical activity of a PI3K and MEK inhibitor combination in *KRAS*-mutant ovarian cancer, for which there is a lack of effective treatment options. We observed a higher ORR in patients with *KRAS*-mutant ovarian cancer compared with a single-agent MEK inhibitor in the same population. A hypothesis might be that PI3K and MEK inhibitor combination therapy is more active in certain *KRAS*-mutant genotypes such as G12V. Although not statistically significant, patients in this study with *KRAS* G12V–mutated ovarian cancers seemed to benefit more from the combination treatment. Emerging evidence in colorectal cancer and NSCLC (26–28) indicates that not all *KRAS*-mutant genotypes are alike in terms of their biology, and may respond differently to the same treatment. However, additional data are required to evaluate this hypothesis. Various questions arise from our data, including whether *KRAS* mutation is a predictive biomarker in low-grade serous ovarian cancer, and whether other histologic subtypes of ovarian cancers with *RAS* mutations will benefit from MEK inhibitor therapy or PI3K and MEK inhibitor combinations. To further investigate sensitivity of low-grade ovarian cancer and the role of *KRAS* mutations and signaling pathways in PI3K and MEK inhibitor combination therapy, additional studies are warranted.

The combination of oral pan-PI3K inhibitor buparlisib and MEK1/2 inhibitor trametinib has an MTD of buparlisib 70 mg and trametinib 1.5 mg daily and an RP2D of buparlisib 60 mg and trametinib 1.5 mg daily in patients with mutant *BRAF*/*RAS* solid tumors. Predominant toxicities of the combination were gastrointestinal and dermatologic, requiring frequent dose interruption and/or dose modification. This oral combination demonstrated promising antitumor efficacy for patients with ovarian cancer with *KRAS*-mutant tumors.

Disclosure of Potential Conflicts of Interest

P.L. Bedard reports receiving commercial research grants from Astra Zeneca, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Roche/Genentech; and is a consultant/advisory board member for Pfizer and Roche. J. Tabernero is a consultant/advisory board member for GlaxoSmithKline and Novartis. F. Janku reports receiving other commercial research support from Novartis. J. Vansteenkiste is a consultant/advisory board member for Novartis. C.D. Britten reports receiving a commercial research grant from Novartis. N.T. Le has ownership interest (including patents) in GlaxoSmithKline. K. Carter and D. Csonka are employees of and have ownership interest (including patents) in Novartis Pharma AG. D. Demanse and M. Peters are employees of Novartis Pharma AG. No potential conflicts of interest were disclosed by the other authors.

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References

1. Britten CD. PI3K and MEK inhibitor combinations: examining the evidence in selected tumor types. Cancer Chemother Pharmacol 2013;71:1395–409.
2. Kullmann F, Hartmann A, Stöhr R, Messmann H, Dollinger MM, Trojan J, et al. KRAS mutation in metastatic pancreatic ductal adenocarcinoma: results of a multicenter phase II study evaluating efficacy of cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in first-line therapy. Oncology 2011;81:3–8.
3. D'Arcangelo M, Cappuzzo F. K-Ras mutations in non–small cell lung cancer: prognostic and predictive value. ISRN Mol Biol. 2012;2012:Article ID 837306.
4. Arrington AK, Heinrich EL, Lee W, Duldulao M, Patel S, Sanchez J , et al. Prognostic and predictive roles of KRAS mutation in colorectal cancer. Int J Mol Sci 2012;13:12153–68.
5. Ascierto PA, Schadendorf D, Berking C, Agarwala SS, van Herpen CM, Queirolo P , et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 2013;14:249–56.
6. Vakiani E, Solit DB. KRAS and BRAF: drug targets and predictive biomarkers. J Pathol 2011;223:219–29.
7. Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, et al. Effective use of PI3K and MEK inhibitors to treat mutant KRAS G12D and PIK3CA H1047R murine lung cancers. Nat Med 2008;14:1351–6.
8. Hoeflich KP, O'Brien C, Boyd Z, Cavet G, Guerrero S, Jung K, et al. *In vivo* antitumor activity of MEK and phosphatidylinositol 3-kinase inhibitors in basal-like breast cancer models. Clin Cancer Res 2009;15:4649–64.
9. Baselga J, De Jonge MJ, Rodon J, Burris HA, Birle DC, De Buck S, et al. A first-in-human phase I study of BKM120, an oral pan-class I PI3K inhibitor, in patients (pts) with advanced solid tumors. J Clin Oncol 2010;28 (Suppl):3003.
10. Bendell JC, Rodon J, Burris HA, de Jong M, Verweij J, Birle DC, et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. J Clin Oncol 2012;30:282–90.
11. Yamaguchi T, Yoshida T, Kurachi R, Kakegawa J, Hori Y, Nanayama T, et al. Identification of JTP-70902, a p15INK4b inductive compound, as a novel MEK1/2 inhibitor. Cancer Sci 2007;98:1809–16.
12. Abe H, Kikuchi S, Hayakawa K, Iida T, Nagahashi N, Maeda K, et al. Discovery of a highly potent and selective MEK inhibitor: GSK1120212 (JTP-74057 DMSO Solvate). ACS Med Chem Lett 2011;2:320–4.
13. Infante JR, Fecher LA, Falchook GS, Nallapareddy S, Gordon MS, Becerra C , et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:773–81.
14. Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, DeMarini DJ, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:782–9.
15. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103–20.
16. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008;27:2420–39.
17. Britten C, Wainberg Z, Tabernero J, Alsina Maqueda M, Leong S, Sessa S, et al. Multi-arm phase 1 dose escalation study of safety, pharmacokinetics, and pharmacodynamics of the dual PI3K/mTOR inhibitors PF-04691502 (oral) and PF-05212384 (IV) in combination with the MEK inhibitor PD-0325901 or irinotecan in patients with advanced cancer. Eur J Cancer 2012;48:109.
18. Grilley-Olson JE, Bedard P, Fasolo A, Blackman S, Cartee L, Baker-Neblett K, et al. A phase I study of the MEK inhibitor GSK1120212 (GSK212) in combination with PI3K/mTOR inhibitor GSK2126458 (GSK458) in patients with advanced solid tumors. Mol Cancer Ther 2011;10:11.
19. Infante JR, Gandi L, Shapiro G, Rizvi N, Burris H, Bendell J, et al.Combination of the MEK inhibitor, pimasertib (MSC1936369B), and the PI3K/mTOR inhibitor, SAR245409, in patients with advanced solid tumors: results of a phase Ib dose-escalation trial [abstract]. In: Proceedings of the 104th Annual Meeting of the American Association for Cancer Research; 2013 Apr 6–10; Washington, DC. Philadelphia (PA): AACR; 2013. Abstract nr LB-147.
20. Kurzrock R, Patnaik A, Rosenstein L, Fu S, Papadopoulos KP, Smith DA, et al. Phase I dose-escalation of the oral MEK1/2 inhibitor GSK1120212 (GSK212) dosed in combination with the oral AKT inhibitor GSK2141795 (GSK795). J Clin Oncol 2011;29:215s.
21. Shapiro G, LoRusso P, Kwak EL, Cleary JM, Musib L, Jones C, et al. Clinical combination of the MEK inhibitor GDC-0973 and the PI3K inhibitor GDC-0941: a first-in-human phase Ib study testing daily and intermittent dosing schedules in patients with advanced solid tumors. J Clin Oncol 2011;29(15 suppl):3005.
22. Tolcher AW, Baird RD, Patnaik A, Moreno Garcia V, Papadopoulos KP, Garrett CR, et al. A phase I dose-escalation study of oral MK-2206 (allosteric AKT inhibitor) with oral selumetinib (AZD6244; MEK inhibitor) in patients with advanced or metastatic solid tumors. J Clin Oncol 2011;29:195s.
23. Farley J, Brady WE, Vathipadiekal V, Lankes HA, Coleman R, Morgan MA, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2013;14:134–40.
24. Janku F, Wheler JJ, Naing A, Falchook GS, Hong DS, Stepanek VM, et al. PIK3CA mutation H1047R is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors in early-phase clinical trials. Cancer Res 2013;73:276–84.
25. Ventura AP, Radhakrishnan S, Green A, Rajaram SK, Allen AN, O'Briant K, et al. Activation of the MEK-S6 pathway in high-grade ovarian cancers. Appl Immunohistochem Mol Morphol 2010;18:499–508.
26. Ihle NT, Byers LA, Kim ES, Saintigny P, Lee JJ, Blumenschein GR, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. J Natl Cancer Inst 2012;104:228–39.
27. Modest DP, Brodowicz T, Stintzing S, Jung A, Neumann J, Laubender RP, et al. Impact of the specific mutation in KRAS codon 12 mutated tumors on treatment efficacy in patients with metastatic colorectal cancer receiving cetuximab-based first-line therapy: a pooled analysis of three trials. Oncology 2012;83:241–7.
28. Tejpar S, Celik I, Schlichting M, Sartorius U, Bokemeyer C, Van Cutsem E. Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. J Clin Oncol 2012;30:357–07.

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A Phase Ib Dose-Escalation Study of the Oral Pan-PI3K Inhibitor Buparlisib (BKM120) in Combination with the Oral MEK1/2 Inhibitor Trametinib (GSK1120212) in Patients with Selected Advanced Solid Tumors

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